

## **Remarks**

This response has been submitted to address the office action of December 20, 2006 regarding the status of claims. After amendment, claims 1-20 remain pending in the present application. Claims 1, 4, 5 and 6 have been amended to address the Examiner's 35 U.S.C. §112, second paragraph rejection. The amendment to the claims has been made to clarify the originally filed claims and to expedite allowance of the instant application. No substantive amendment to the claims has been made to place the application in condition for allowance. No amendment has been made to distinguish over the art of record. Support for the amendment to the claims may be found throughout the originally filed application and claims and more specifically at page 10, lines 10-12 (for stabilized compositions), at page 10, second full paragraph (lines 8-11), at page 13, second and third full paragraphs. No new matter has been added by way of this amendment. No substantive change has been made to this resubmission.

The Examiner has rejected originally filed claims 1-20 under 35 U.S.C. §112, second paragraph, §102(b) and §103. For the reasons which are set forth in detail herein, it is respectfully submitted that the cited reference(s) do not anticipate the present invention, do not render the present invention obvious and, after amendment to address the §112, second paragraph rejection, the claims are now in condition for allowance.

### **The §112, Second Paragraph Rejection**

The Examiner rejected claims 1, 4, 5 and 8 (actually claim 6) as being invalid under 35 U.S.C. §112, second paragraph for the reasons which are stated in the office action on pages 2-3. Applicants have amended claims 1, 4, 5 and 6 to address the rejected language in compliance with the requirements of 35 U.S.C. §112, second paragraph. Note that claim 1 now recites that the pH is stabilized, claim 4 recites "surfactant" rather than "surface active agent", the term "comparable" in claim 5 has been changed to "the same or greater than" and the term "or more" in claim 6 (not claim 8 as the Examiner had originally indicated) has been changed to "about twenty-six months". It is respectfully submitted that each of the amended terms addresses the

Examiner's concerns raised under 35 U.S.C. §112, second paragraph and the amended claims are now in full compliance with the requirements of 35 U.S.C. §112.

**The Rejection of Claims 1-20 Under 35 U.S.C. §102(b)**

*The Rejection of Claims 1-9, 14, 16 and 20 As Being Anticipated by Xu, et al. and Claims 1-20 As Being Anticipated by Benjamin, et al.*

The Examiner has rejected claims 1-9, 14, 16 and 20 as being anticipated by the disclosure of Xu, et al., *Journal of Applied Microbiology*, 90, 523-529, April, 2001 ("Xu, et al.") and claims 1-20 as being anticipated by the disclosure of Benjamin, et al., US Patent Application Publication US2002/0136750 ("Benjamin, et al.") for the reasons which are set forth in the August 30, 2006 office action on pages 4-7. For the reasons which are set forth hereinbelow, Applicants respectfully submit that the present invention is not anticipated by the disclosure of Xu, et al. or Benjamin, et al. for the simple reason that neither reference discloses all of the claimed elements of the present invention.

The present inventive compositions differ from the past teachings because, in the present invention, the nitrite salt and acidifier can be initially combined and the resulting system can thereafter provide long-term antimicrobial properties, for at least weeks or months after their mixture. This is reflected in the claimed concentration of nitrite in the form of nitrous acid which is important for maintaining long term activity in the present invention. This is not taught or suggested by the prior art of record. In contrast to the present invention, the prior art references which teach combined nitrite/acid systems require that the systems be mixed-and-used on site (Benjamin *et al.*) or the equivalent, as shown by Xu *et al.*, (for salivary nitrites that contact an acidic stomach). The prior art and in particular, Benjamin *et al.*, clearly state that the mixtures then continuously lose efficacy after preparation, in contrast to the present invention.

For example, Benjamin *et al.*, relate the germicidal action of disclosed compositions to gaseous nitrogen oxides which form immediately upon combination of the nitrite and acid, and have a short lifetime in the system. The present invention stands in stark contrast to the

disclosure in Benjamin, et al., in that the present invention can provide continued high level germicidal activity long after the nitrogen oxides have dissipated, and can therefore be used as one-phase systems for extended periods. This is possible by setting the boundaries on the acidities of the system in terms of maximum and minimum fractions of the nitrite ion that can exist in the nitrous acid form, which is claimed and is clearly not disclosed in the cited prior art.

With respect to the disclosure of Xu, et al., the teachings there are based on experiments that were run on acid/nitrite systems at concentrations that are *orders of magnitude below* that claimed in the present application, and thus the teachings of Xu, et al. are not realistically projectable to the present application. Moreover, Xu *et al.* conclude that, under the conditions of their studies, the nitrogen oxides are not the primary source of bactericidal effects. In fairness, Xu, et al. cannot be cogently said to even remotely anticipate the present invention.

Note that Applicants do not contest that Xu *et al.* and Benjamin *et al.* teach that the direct combination of certain acids and nitrite ion, and its salts, provide significant bacterial effects. But the Examiner apparently confuses stability of pH in a solution with the long-term germicidal activity of the present application, which is provided for by the claim limitations. See the Examiner's statement on p.5, lines 7, 8 of the August 30, 2006 office action where he states that "...it is expected to remain stable because citrate-phosphate is a strong buffer in acidic conditions", with the claimed long-term germicidally-stable solutions of the present invention. In point of fact, the Examiner's reference to citrate-phosphate buffers being pH-stable is inconsistent with his subsequent citation of the changing, and decreasing pH values of the inventive compositions, "...the pH of the composition either remains relatively constant at an initial value of around 3.75 or lower, or decreases from said initial value...to a value as low as around 2.5 over a period of at least about two days...." (office action on p.5, lines 9-12). The very nature of buffers, specifically acid buffers as taught by the cited prior art, is to maintain the pH of a system so as to resist *alkaline* or pH raising factors which may otherwise drive the pH higher in the direction of neutrality (pH of 7). Buffers do this by using the solutions' available  $H^+$  ions and thereafter the  $H^+$ - generating capacity of its unionized molecules. Ultimately, as the solution trends toward or continues to be alkaline- challenged and the buffering capacity is consumed, the pH of the system will rise rather than lower as in the case of the presently claimed

compositions. The downward pH drift of the pH of the presently claimed compositions is characteristic as set forth in claim 1, wherein “.. the molar percentage of nitrite ion in the composition in the form of nitrous acid is greater than about 35% but less than about 95% of the total nitrite ions present in the composition..”. As a result of conforming with that characteristic, “..the composition exhibits cidal activity against microorganisms for a period of at least several months after formulation..”

Unlike buffer solutions, in which  $H^+$  ions are gradually consumed, the compositions of the present invention at the specified range of nitrite ion in the form of nitrous acid of >35% - <95% as claimed, have the ability to slowly and continuously generate  $H^+$  ions, by virtue of the gradual shift of the disproportionation reaction shown by the following equation:



where the +3 valence nitrite nitrogen shifts to the +2 and +5 states. The function of the buffering acids in the present compositions, in stark contrast to the prior art teachings, is simply to reduce the pH of the system to the point where the acidity of the solution facilitates the conversion of approximately 35% -95% of the nitrite ion to its corresponding nitrous acid form. These acids are in no way responsible for a subsequent downward pH shift of the system. [Note that in a closed, non-alkaline challenged environment, the slow degradation of the above system, liberating additional  $H^+$  ions, can result in a slowly decreasing pH, generally inversely proportional to the relative nitrous acid/nitrite ion ratio. At lower ratios the solution is more pH stable; at higher ratios the downward drift is more favored.]

The Examiner argues that the presently claimed invention is not novel (novelty residing at least partially in that the composition exhibits cidal activity against microorganisms for extended periods) by his statement that “(t)he prior art compositions ... are expected to show such functional properties because they are deemed to be the same compositions comprising the same ingredients. The Examiner’s statement, however, is contrary to the explicit teachings of the prior art, including that of Benjamin *et al.*, to which the Examiner referred in the subsequent paragraphs of the August 30, 2006 document. [see the following section.]

**Benjamin et al.**

This references teaches the criticality of:

- a)- separation of acid and nitrite before direct use, and
- b)- the presence of nitrogen oxides for germicidal action.

Benjamin, et al. clearly teaches that the initial composition of nitrite and acid will rapidly change by the degradation of the nitrous acid, then formed, into NO and NO<sub>2</sub>. Within a short period, the resulting composition is no longer that of the initial combination. To illustrate this point, Benjamin *et al.* specifically indicate that the nitrite source and the acid source must be separately maintained, and then mixed at the site of application. This, they teach, is because the active NO and NO<sub>2</sub> agents, responsible for germicidal activity, have a short lifetime.

See claim 1 of Benjamin which teaches:

A pharmaceutically acceptable acidifying agent in an amount sufficient to reduce the pH of an environment of use to below pH4, and

A pharmaceutically acceptable source of nitrite ions or a nitrate precursor therefore; wherein said acidifying agent and said source of nitrite ions or nitrate precursor are separately disposed in respective pharmaceutically acceptable carriers for admixture at the intended environment of use to release NO or NO<sub>2</sub> ions. [Emphasis added].

Similar language is found in Claim 7 of Benjamin, et al.: “A dosage form...for the treatment..comprising an admixture of nitrogen oxides generated at the environment of use. “In fact, note particularly **paragraph 0035** of Benjamin, et al., which reads in its entirety:

*If the pharmaceutically acceptable acidifying agent and the pharmaceutically acceptable donor of nitrogen oxides, or a precursor therefor were brought into contact before reaching the site of biological action the efficacy of the treatment is diminished as the nitrogen oxides become progressively more inactive with time.*

In Benjamin *et al.* 's **Example 4**, they illustrate how short the active lifetimes of their compositions are, once mixed. The peak release of both NO and NO<sub>2</sub> of the Benjamin, et al. compositions occur in about 4 minutes after combination of the nitrite and acid, and then drop off rapidly thereafter. These two gasses, being highly volatile, rapidly dissipate to the environment following their creation, which is consistent with their being combined at the site of use. This stands in stark contrast to the present invention.

Throughout the Benjamin *et al.* document it is continuously noted that the nitrogen oxides are the key to the antimicrobial activity of their system, as in:

Document reference		Statement
Page	Paragraph	
1	0001	The present invention <b>relates in one aspect to acidified nitrite as an antimicrobial agent</b> , and to a <b>complex of nitrogen oxides arising from the interaction of nitrite and acid</b> as an antiviral composition... Such nitrogen oxides include in particular NO which is of importance particularly if acidified.
1	0014	We have now found ...that <b>nitrite</b> at concentrations up to 4%..when <b>mixed with an organic acid....reacts to product oxides of nitrogen which are effective in killing infectious organisms</b> ...including fungi, yeast, bacteria and viruses.
2	0024	..there is provided a dosage form for the treatment of <b>bacterial, virus, or fungal conditions</b> ... which comprises:
2	0025	a pharmaceutically acceptable <b>acidifying</b> agent...
2	0026	a pharmaceutically acceptable source of <b>nitrite ions</b> ...

Document reference		
2	0027	wherein said <b>acidifying agent</b> and said source of <b>nitrite ions.....are <u>separately disposed...</u> for admixture at the intended environment</b> of use to release NO or NO <sub>2</sub> ions
2	0029	..the <b>acidifying agent</b> and the source of <b>nitrite ions...are separately disposed..for admixture to release NO<sub>2</sub> or NO ions at the environment of use.</b>
3	0035	....”were brought into contact before reaching the site...the efficacy is diminished as the nitrogen oxides become progressively more inactive with time.”
3	0036	....the pharmaceutically acceptable <b>acidifying agent</b> , the <b>donor nitrogen oxides or a precursor therefor are separately disposed.....</b>
4	0050	..the donor of the <b>nitrogen oxides...</b> (and many other such references to such oxides)

It is respectfully submitted, based upon the above presentation, that Benjamin, et al. in no way anticipates the present invention.

**Xu et al.**

Xu, et al. is directed to studies in which the authors duplicated conditions that occur in the stomach following ingestion of salivary nitrite. They report that normal levels of nitrite nitrogen in the stomach are about 1 mg/liter, corresponding to nitrite levels of about 3.3 mg/liter [corresponding to 0.00033%]. Since nitrite levels might rise to as much as 20 mg/liter of nitrite

nitrogen, they set up their studies to accommodate higher levels as well, by using 1- and 10-mg/liter as nitrite nitrogen, equivalent to nitrite concentrations of 0.00033% and 0.0033%. Based on the findings from those studies, at those specific conditions, the authors concluded that the observed bactericidal effects were not primarily related to nitric oxide and nitrogen dioxide. This teaching stands in direct contract to the drawn by Benjamin *et al.* for the more highly concentrated systems of their application. In the Benjamin, et al. case (see claim 12) the alkali metal nitrite concentrations constitute “0.5% to 30% by weight of the total dosage form.” [0.33% - 20% of nitrite, assuming the common Na salt]. The difference in conclusions drawn between Xu, et al. and Benjamin, et al., thereby opens the question of how similar are acid/nitrite chemistries at the widely disparate concentrations of the two prior art references. The answer is not very. Indeed Xu, et al. discloses nitrite levels *far below* that of the present invention and although the Benjamin *et al.* levels somewhat approximate the nitrite levels taught in the present application, as outlined on page 14 of the present specification, the levels of the present invention are clearly quite distinguishable *i.e.*,:

The present invention:

<u>percent by weight of metal nitrite</u>	<u>as nitrite alone</u>
less than about 1.0,	0.67%
preferably about 0.01 to about 0.75,	0.067 - 0.50%
more preferably 0.03 to about 0.70,	0.20 - 0.47%
and even more preferably from about 0.05 to about 0.50	0.033% - 0.33%

In contrast:

Benjamin *et al.* levels = 0.5% - 20% as metal nitrite

The present invention levels = 0.01% - 1.0% as metal nitrite

Xu *et al.* levels = 0.00050% - 0.0050% as metal nitrite

The lowest concentrations of the Benjamin *et al.* systems barely bracket the highest concentrations of the present invention. And the systems of the present invention can be up to *2,000 times higher in concentration* than are those disclosed by Xu *et al.*, and no less than at least twice the highest concentration disclosed by Xu *et al.*



In summary, neither the teachings of Benjamin *et al.*, nor the teachings of Xu *et al.*, anticipate the long-acting disinfecting nitrous acid compositions which form the basis of the pending application. In contrast to the present invention, Benjamin, et al. calls for an on-site mixture and application, and *in situ* generation of nitrogen oxides to provide germicidal action during short generation times, and Xu, et al. discloses compositions which are based on much less concentrated, transient systems, not the compositions according to the present invention. The chemistry of the composition of Xu, et al. do not extrapolate to the present inventive compositions; especially since the conclusions drawn by Benjamin *et al.*, and those cited by the authors of Xu *et al.* regarding the source of germicidal action are so starkly different. In particular, the “Significance and Impact of the Study” by Xu *et al.* is given in very narrow terms, as “The potential role of nitrite as an antimicrobial substance in the stomach may be of some importance in the ecology of the gastrointestinal tract and in host physiology” with no anticipation that acid/nitrite combinations with at least an order of magnitude higher concentrations (as in the present invention) would be generally useful over protracted time periods as a broad-spectrum antimicrobial agent.

It is respectfully submitted that Applicants have cogently pointed out that the present invention is not anticipated by either of Benjamin, et al. or Xu, et al.

### **The Rejection of Claims 10-13 15 and 16-19 Under 35 U.S.C. §103**

The Examiner has rejected originally filed claims 10-13, 15 and 16-19 under 35 U.S.C. §103 as being unpatentable over Xu, et al., in view of Kross, et al., U.S. patent no. 6,063,405 (Kross, et al.) for the reasons which are set forth in the August 30, 1006 office action pages 8 and 9. Essentially it is the Examiner’s position that the disclosure of Xu, et al., can be combined with the teachings of Kross, et al. to provide the present invention. Applicants respectfully traverse the Examiner’s rejection.

The stark differences between the presently claimed compositions and the compositions which are disclosed by Xu, et al. have been discussed in great detail hereinabove. In short, Xu,

et al., do not disclose compositions which are even remotely related to the present invention in that the concentration of nitrite and nitrous acid of Xu, et al. is significantly different than in the present invention and the ratio of nitrous acid to total nitrite in the composition falls within specific percentages, which are markedly distinguishable over the compositions of Xu, et al. which are prepared to mimic compositions in the gastrointestinal tract. There is absolutely no disclosure in Xu, et al. of the present compositions, or the requirement for certain concentrations of a nitrite salt or a relative percentage of nitrous acid to total nitrite salt in the composition which provides a stable composition that exhibits substantial germicidal activity over long periods of time. There is absolutely no suggestion in Xu, et al. of the present invention and there is simply no motivation taught to provide or pursue the instant compositions. The present invention is clearly non-obvious over Xu, et al.

Turning to Kross, et al, this reference, is perhaps inapposite to the present invention, inasmuch as it teaches certain chlorous acid/chlorite systems for disinfecting meat carcasses. There is absolutely no disclosure in Kross, et al. of a nitrous acid/nitrite system and there is absolutely no suggestion of the present compositions which are based upon nitrous acid/nitrite. Given that Xu, et al. clearly fail to motivate the present compositions, and Kross, et al. are not even related to the same chemical system as in the present invention, it cannot be cogently asserted that the presently claimed compositions are obvious over the disclosure of Xu, et al., in view of Kross, et al. The argument that the Examiner makes that one could take the teachings of Xu, et al., regarding compositions which do not teach the limitations of the present invention or desirability of the chemical characteristics of the present invention and somehow combine that disclosure with Kross, et al., which is directed to a *different chemical system* than the present invention, to produce the presently claimed invention is simply not a cogent argument and should be withdrawn. The presently claimed invention is clearly non-obvious over the teachings of Xu, et al., in view of Kross, et al.

For the above reasons, Applicant respectfully asserts that the claims set forth in the amendment to the application of the present invention are now in compliance with 35 U.S.C. Applicants respectfully submit that the present application is now in condition for allowance and such action is earnestly solicited.

Applicants have not added nor cancelled any claim. No fee is therefore due for the presentation of this amendment. If a determination that any fee is due or any overpayment is made, please charge/credit Deposit Account No. 04-0838. Should the Examiner wish to discuss the present application in an effort to advance its prosecution, the undersigned attorney may be reached at the telephone number set forth hereinbelow.

Respectfully submitted,

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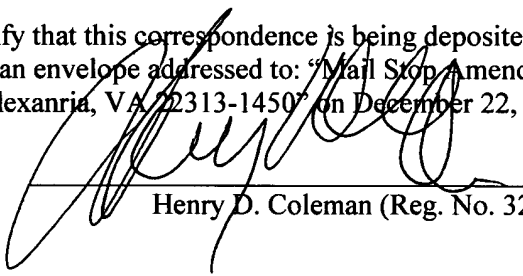
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